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Independent Sun Care Product Screening for Benzene Contamination

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Introduction

Benzene is a well-documented Group 1 carcinogen and environmental hazard.[1] Even in trace amounts, benzene is known to pose a health risk from exposure routes that include inhalation, ingestion, dermal absorption, and skin or eye contact.[2]

Health care professionals recommend sunscreen to prevent skin cancer, and reapplication is recommended every hour, which is more frequent than recommendations in most package directions.[3] Consumers can choose from many sunscreen formulations, including lotions and aerosol sprays, and it is estimated that more than 11,000 different sunscreen products are registered in the United States.[4] Chemical UV-blocking agents, including avobenzone, oxybenzone, octisalate, octinoxate, homosalate, octocrylene, and physical UV-blocking agents, including zinc oxide, are regulated by the U.S. Food and Drug Administration (FDA) as active pharmaceutical ingredients (API), rendering sunscreens as regulated drug products. Other topical products, such as those used after sun exposure, are typically regulated in the United States as cosmetics under the Federal Food, Drug, and Cosmetic Act (FDCA) and Fair Packaging and Labeling Act. Benzene is restricted by the FDA to 2 parts per million (ppm) only in cases where its use in manufacturing is unavoidable and the drug product constitutes a significant therapeutic advance. In all other cases, which ostensibly include sunscreens, FDA guidance is to avoid benzene altogether. The National Institute for Occupational Safety and Health recommends that workers who are expected to be exposed to benzene at concentrations 0.1 ppm or above for 10 h, or 1 ppm for 15 min, wear protective equipment.[2] As stated in a 2010 review of benzene health effects, "...[A]ll exposures constitute some risk in a linear, if not supralinear, and additive fashion."[5] Furthermore, benzene exposure, whether occupational or infrequent and from a variety of environmental sources, has been linked to blood cancers.[6,7] For purposes of this study, concentrations greater than 2.0 ppm and concentrations of 0.1 ppm–2.0 ppm are used as brackets of concern. However, benzene at any concentration in consumer products could pose a risk to consumers and the environment.

Benzene was first detected during routine testing in two sunscreen products. To determine the scope of the potential problem, Valisure LLC (hereinafter Valisure) followed up with a market assessment of commonly available sun care products by independently sourcing and testing different brands and formulations. Benzene was detected in many sunscreen and after-sun care products, and Valisure notified the FDA through a citizen petition filed on 24 May 2021.[8] To better determine the scope of contamination, Valisure continued to analyze sunscreen and after-sun care products through a crowdsourced study that allowed for broader product sampling and facilitated access to sun care products that were sold prior to lab sourcing efforts.

Methods

Products for the citizen petition were independently sourced by Valisure and purchased between September 2020 and May 2021 ($n = 293$). Multiple samples of some products were purchased if available in different lots to determine lot-to-lot differences in products, but there were no duplicate lots in the lab-sourced (LS) samples. A total of 368 crowdsourced (CS) samples were received from 32 U.S. states and two regions of Canada between late May and early August 2021. Samples from Canada represented 2% of all CS samples. CS samples were accepted in their original containers, and many were unsealed or appeared partially depleted, suggesting consumer use. Overall, 18% of CS samples and 0% of LS samples were expired at the time of testing, and 18% of LS samples and 12% of CS samples did not have discernible expiration dates. These samples were included because they were representative of products used by individuals. In addition, 16 of the 368 CS samples were duplicate lots.

Detailed analytical methods are provided with replicate measurement data and sample information as part of Valisure's citizen petition to the FDA.[8] In brief, headspace sampling with gas chromatography–mass spectrometry (GC-MS) detection (Agilent 7697A headspace autosampler, 7890B GC, and 5977B MS) was used following USP <467> Residual Solvents Procedure A, modified to optimize benzene sensitivity and decrease run time. Analysis of reference standards for select sunscreen APIs, avobenzone, oxybenzone, octisalate, octinoxate, homosalate, and octocrylene (Sigma-Aldrich) using the aforementioned methodology revealed trace benzene detection for avobenzone, only amounting to 25 ng/sample or 0.2 ppm in reference powder labeled as 98.4% pure. Trace levels of benzene were detected in solvent blanks, accounting for less than one-third of that in the lowest calibration standard (10 ng or equivalent to 0.02 ppm in products). The average triplicate solvent blank peak area was subtracted for all calibrations, quality controls, and samples in each analytical batch. Solvent blanks were also analyzed in sequence after the highest concentration calibration standard and the sample with the highest benzene detection, and no carryover was detected. Representative samples were spiked with a known amount of isotopic labeled (d3) benzene to monitor overall recovery. Matrix spike testing was performed by spiking U.S. Pharmacopeia (USP)-certified benzene at low [lower limit of quantitation (LLOQ)], medium (midpoint of calibration), and high (80% of the highest calibration) into representative lotion, cream, and spray samples.

The lower limit of detection (LLOD) using sunscreen matrices was 0.01 μg, and the LLOQ was 0.025 μg, equivalent to 0.05 ppm in samples. Concentration results are reported in micrograms of benzene detected per gram of product tested or parts per million. For figure categories, "spray" includes aerosol and pump

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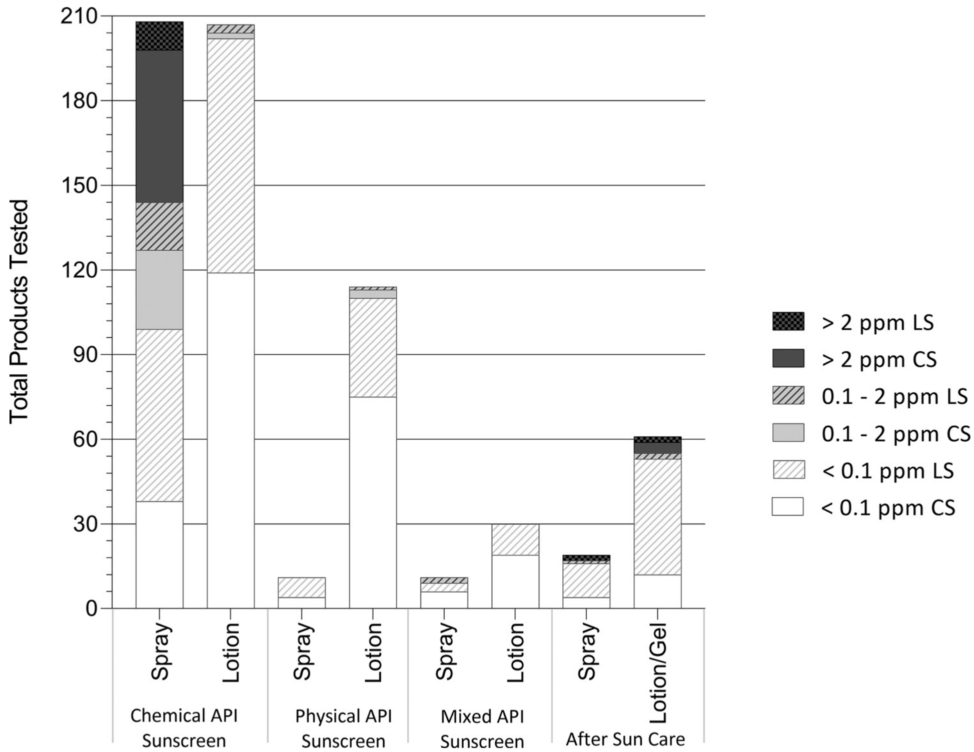

Figure 1. The number of products tested that fall into concern categories for benzene detection of greater than 2.0 ppm (>2.0 ppm) or between 0.1 and 2.0 ppm (0.1 − 2.0 ppm) in comparison with <0.1 ppm or not detected (<0.1 ppm or ND) separated by product type and distinguished between lab-sourced (LS) and crowdsourced (CS) by shading. Note: ND, not detected.

spray products and "lotion" includes products labeled as such, as well as those labeled cream, gel, and stick.

Chi-squared contingency table analysis was performed for LS samples and used to determine correlation between product type (chemical API sunscreen, physical API sunscreen, mixed API sunscreen and after-sun care) and parts per million categories. Two levels of contingencies were examined: chi-squared for all 4 filter types and chi-squared for each pair of filter types. Similarly, contingency analysis was performed for LS samples to determine correlation between individual active ingredients (avobenzone, homosalate, octisalate, octocrylene, oxybenzone, octinoxate, zinc oxide, titanium dioxide, lidocaine, and "cosmetic" for after-sun care products where the active ingredient was not specified) and parts per million categories and between formulation (spray and lotion) and parts per million categories.

Results and Discussion

A total of 661 (293 LS, 368 CS) sunscreen and after-sun care samples (e.g., bottles) were screened for benzene, representing 108 unique brands and at least 406 unique Universal Product Codes (UPCs); 43 (1 LS and 42 CS) samples did not have UPCs on the packaging, so as many as 449 UPCs were tested, and 66 of the UPCs were represented two or more times, with one shared by 20 (6 LS, 14 CS) samples. Benzene was most frequently detected at concentrations greater than 2.0 ppm in chemical spray formulations and after-sun care products. Out of 661 product samples (293 LS, 368 CS), 192 (78 LS, 114 CS) samples had detectable levels of benzene, 61 samples (38 LS, 23 CS) had detection of benzene below the LLOQ, 59 samples (26 LS, 33 CS) contained benzene in concentrations between 0.1 ppm and 2.0 ppm, and 72 samples (14 LS, 58 CS) contained benzene in concentrations greater than 2.0 ppm (see Figure 1).

The authors acknowledge the limitations of sampling. For the LS samples, sourcing from large pharmacy chain stores and online vendors may limit the representation of products from smaller vendors. Physical or mixed physical and chemical active ingredient spray products were not well represented in this screen and warrant further study. All LS products were tested prior to expiration, although, notably, the expiration date could not be determined by visual inspection for 99 (15%) samples. LS sample results published in the Valisure citizen's petition may have influenced the choice of sunscreens and after-sun care products individuals submitted as crowd sourced samples. The UPC with the highest number of LS bottles (6) also had the highest number of CS bottles (14), and 166 (45%) of the 368 CS bottles were from the company with the highest number of LS samples with greater than 2.0 ppm benzene. Due to the potential bias effect of LS results on CS sampling, CS samples were omitted from contingency analysis.

Benzene detection described here was overall not strongly correlated with active ingredient [$X^2(18, n=293)=10.6$; $p=0.83$], or with product type [$X^2(6, n=293)=9.21$; $p=0.16$]. The strongest correlation for comparing two active ingredients at a time was for oxybenzone and zinc oxide, which showed zinc oxide, a physical sunscreen filter, was associated with lower benzene detection [$X^2(2, n=56)=7.05$; $p=0.029$]; however, some samples containing zinc oxide did contain detectable levels of benzene. For product types, the chi-squared analysis suggested the parts per million category may depend on product type when chemical API sunscreens and physical API sunscreens are considered [$X^2(2, n=217)=6.36$; $p=0.042$]. In contrast with active ingredients or product types, the proportion of samples in benzene parts per million categories differed significantly by formulation (spray or lotion) [$X^2(2, n=293)=33.2$; $p=0.0000096$], and even further by the specific combinations of formulation

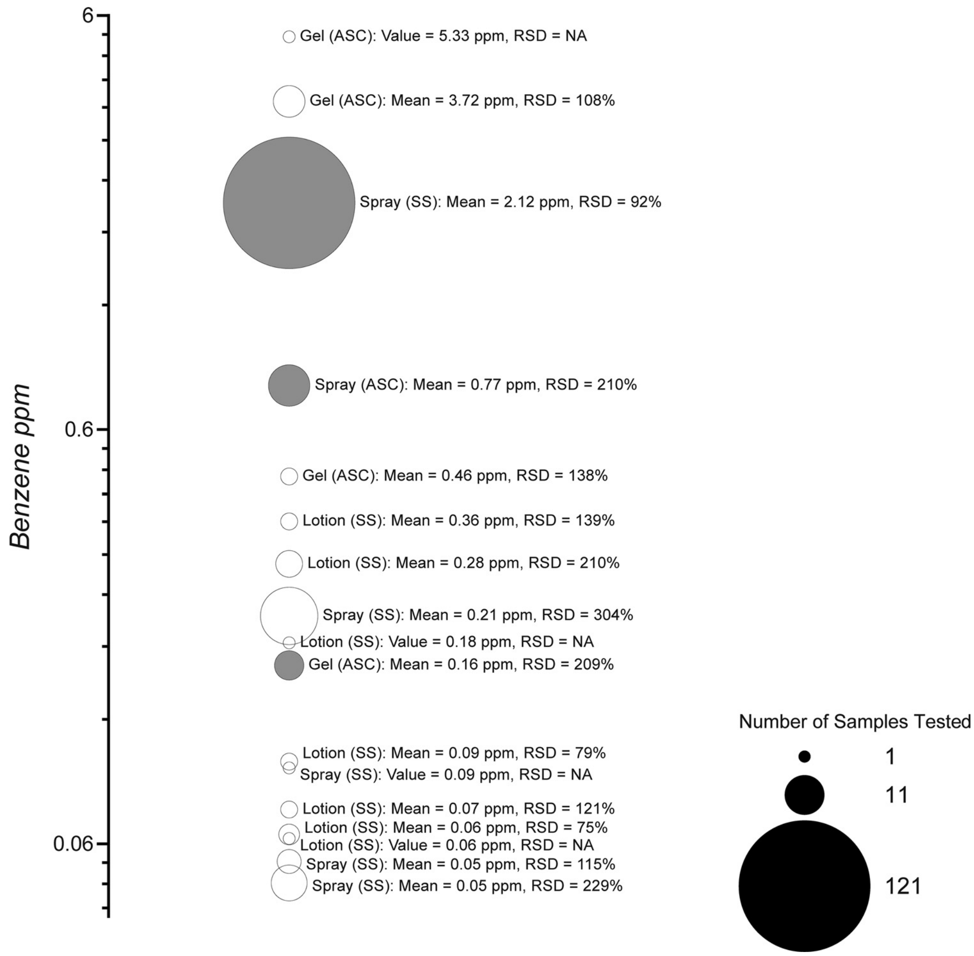

Figure 2. All products tested with benzene above the limit of quantitation (LOQ) when grouped by company and product type (spray, lotion, or gel) with average and relative standard deviation (RSD) when $n > 1$ or values when $n = 1$ are reported. The number of products tested in each group is represented by circle size. Companies that have recalled or removed products from the market in 2021 for benzene contamination are shown in gray. Note: ASC, after-sun care; SS, sunscreen.

and product type [$X^2(14, n = 293) = 48.4$; $p = 9.8 \times 10^{-9}$]. In particular, chemical-filter sunscreen sprays and after-sun care sprays were observed to have more than 2 ppm in higher proportions than others. The consumer products industry likely has many points of vulnerability to benzene contamination, including aerosol propellants or other petroleum industry-derived inactive ingredients, gelling agents like carbomers, and potentially from unlabeled ingredients that the ingredient "fragrance" comprises.

Since public notification through the citizen petition, authors are aware of three companies that took action to remove or recall products due to benzene contamination and an FDA document detailing aerosol sunscreen test results from one company that states, "Benzene results ranged from 11.2 to 23.6 ppm."[9] These values are approximately two to four times higher than Valisure's highest detected level for similar products. Lots tested in duplicate had consistent results (the highest RSD observed for a lot tested two or more times was 22%), whereas tested samples with the same UPCs had more inconsistent results (the lowest RSD observed for a UPC tested 10 or more times was 60%). When tested samples were averaged by company and product type, RSD ranged from 75% ($n = 3$) to 304% ($n = 23$). These data and the variability across samples with the same UPC and marketed by the same companies (see Figure 2) underscore the need for batch-level quality surveillance of sun care products and the complexity of these types of consumer product contamination issues. In December 2021, the FDA formally alerted drug manufacturers to the risk of benzene contamination and requested increased testing.[10] Further surveillance of consumer products and investigation of these environmental and public health findings is warranted.

Acknowledgments

Valisure is an independent laboratory accredited to International Organization for Standardization ("ISO/IEC") 17025:2017 standards for chemical testing. Valisure's mission is to help ensure the safety and quality of medications and healthcare products before they reach consumers. AH and NZ contributed equally to this work.

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